Calcium Kinetics During Spaceflight

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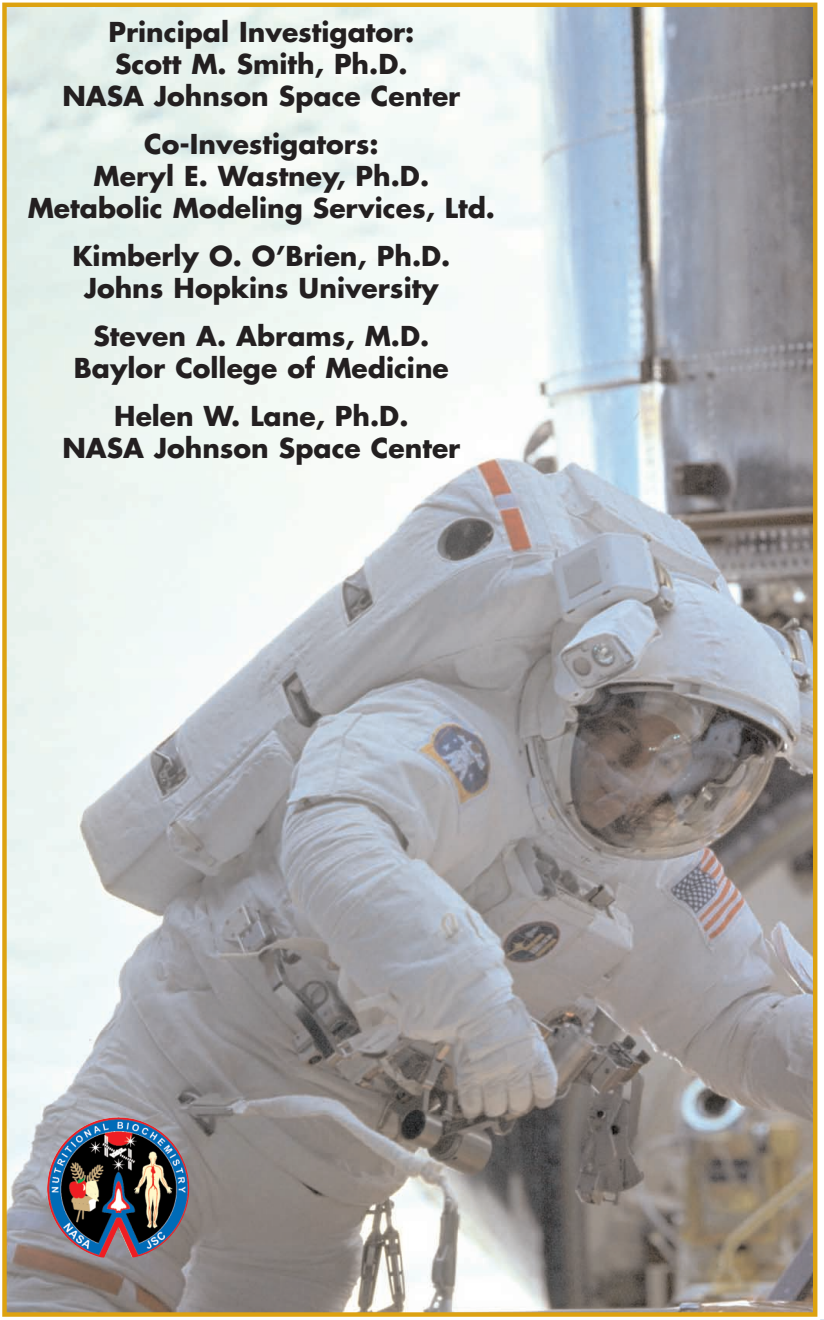


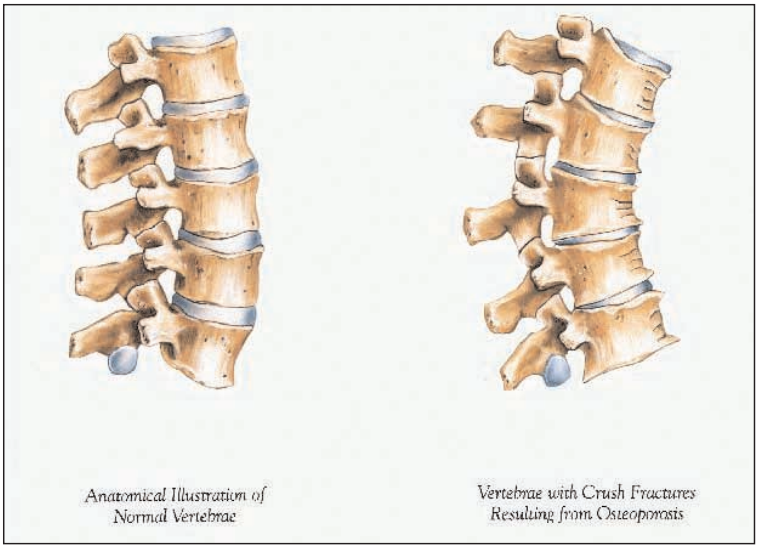
Background

Calcium is lost from bones during weightlessness (1, 2). This phenomenon is greatest in weight-bearing bones (e.g., ankles, hips, spine), as demonstrated in the Skylab missions of the 1970s (2) and more recently, in crews on the Russian space station Mir (3). Understanding precisely how the spaceflight environment induces bone loss, and finding ways of counteracting that loss, represent significant challenges for long-term space exploration. A better understanding of bone loss during spaceflight could also increase our understanding of the causes and treatment of bone diseases on Earth (e.g., osteoporosis).

Bone and Calcium Metabolism During Spaceflight

Insights into the mechanisms underlying bone loss come from the study of calcium metabolism, and from factors that are known to regulate bone and calcium metabolism. Key among these factors are parathyroid hormone, calcitonin, and vitamin D. Together, these factors regulate calcium homeostasis by modulating intestinal calcium absorption, urinary calcium excretion and bone remodeling (the processes of bone building or deposition and bone degradation or resorption).

The pathways of normal calcium movement in the body and some of the factors that regulate calcium metabolism



Anatomical Illustration of Normal Vertebrae

Vertebrae with Crush Fractures Resulting from Osteoporosis

are shown in Figure 1. The NASA studies described here measure many of these in order to better understand bone and calcium metabolism during spaceflight.

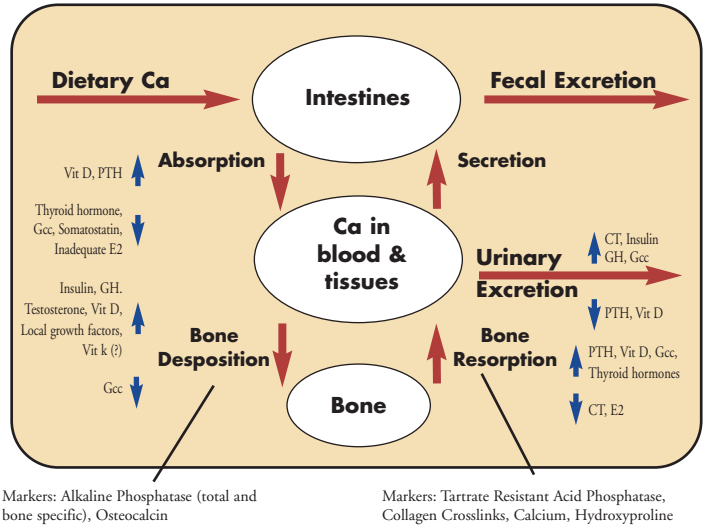


Figure 1. Pathways of Normal Calcium Movement (adapted from reference 4). Abbreviations: CT=calcitonim, E2=estrogen, Gcc=glucocorticoid hormones, GH=growth harmone, PTH=parathyroid hormone, Vit D=active vitamin D

During the Skylab missions, calcium excretion (both urinary and fecal) was increased when compared to measurements taken before flight (1,2). This resulted in a net loss of calcium in the body. Not only is this problematic for bone, elevated urinary calcium can also increase the risk of forming kidney stones (5). Bloodionized calcium and pH do not seem to change during short duration (i.e., shuttle) spaceflight (6).

Vitamin D plays an important role in calcium absorption and metabolism. Vitamin D is initially converted to its hydroxylated form, 25-hydroxyvitamin D, which is then activated in the kidney via hydroxylation, to 1,25-dihydroxy-vitamin D. 1,25-Dihydroxyvitamin D, a major calcium regulatory hormone, and acts primarily to increase intestinal absorption of calcium, and also affects bone resorption.

Sunlight, specifically ultraviolet radiation, is a significant

source of vitamin D for people on Earth. Spacecraft are heavily shielded to reduce crewmembers' exposure to the harmful types of radiation. Thus, lack of ultraviolet light during spaceflight may decrease vitamin D pools in the body, which poses a concern for lengthy missions. Vitamin D levels in serum were lower during spaceflight, when compared to preflight levels, for the three crewmembers aboard the Mir-18 mission (*7*).

Other markers of bone metabolism include indices of bone formation and bone resorption. Bone-specific alkaline phosphatase, a bone formation marker, tended to decrease during Mir missions (*7*). Collagen is the major structural protein of bone. The presence of collagen breakdown products (e.g., pyridinium crosslinks, n-telopeptide) in urine provides a sensitive index of bone resorption. Excretion of these markers is more than doubled during spaceflight, when compared to preflight levels (Figure 2), indicating increased levels of bone breakdown during flight.

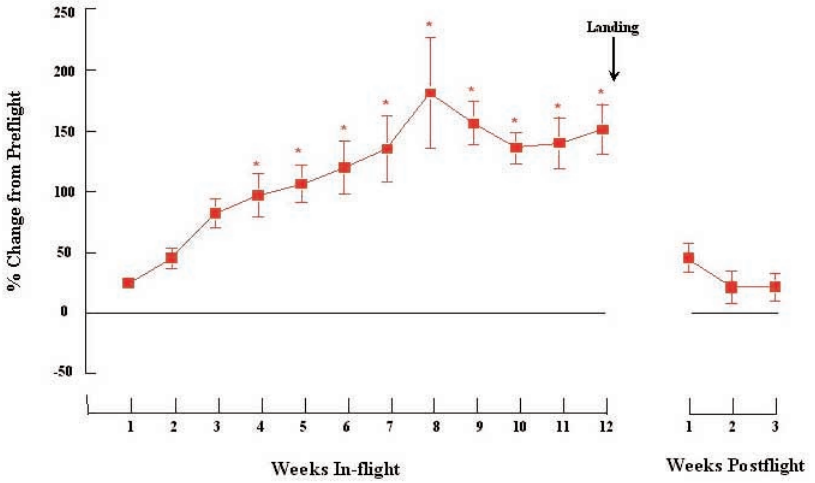


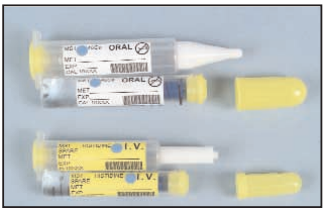
Figure 2. N-Telopeptide excretion during Skylab 4 (Reference 8)

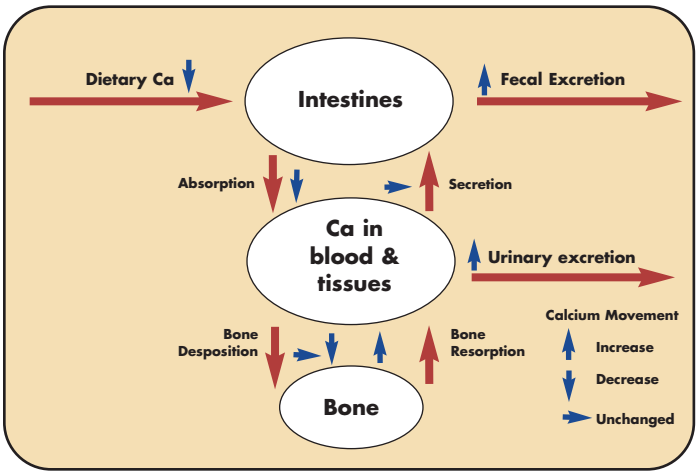
Calcium Kinetics

Understanding the regulation of bone and calcium metabolism during spaceflight will be critical for identifying

and developing methods for counteracting the flight-induced bone loss. Measurements of blood and urine markers of bone metabolism provide useful information about calcium homeostasis at a particular time. However, the ability to monitor calcium movement in and out of the various storage pools throughout the body (blood, bone, etc.) would allow much more detailed and dynamic studies of how the regulatory systems are functioning over time. To address this in crewmembers during flight, we use state-of-the-art tracer techniques to measure calcium kinetic changes before, during, and after spaceflight.

Calcium kinetic studies involve the use of two stable (i.e., nonradioactive) isotopes of calcium, one of which is administered orally and the other intravenously. The appearance and disappearance of these isotopes in biological samples (e.g., blood, urine, saliva, and feces) are documented over the days and weeks following the administration of isotopes. These will need to be specially packaged for use during





In weightlessness
- bone break-down (resorption) increases
- bone formation (deposition) may increase

Figure 3. Hypothesized changes in calcium metabolism during spaceflight

weightlessness.Mathematical modeling techniques are used to monitor the movement of calcium through the body compartments using software developed at the National Institutes of Health (9). Thus, we can determine rates of calcium absorption, urinary and fecal excretion and most importantly, the rates of bone calcium deposition and bone calcium resorption. The hypothesized changes to calcium and bone metabolism during spaceflight are shown in Figure 3.

Previous Research

In-flight determinations of calcium kinetics have been conducted with 6 crewmembers, 3 from the Mir-18 (Figure 4) mission in 1995 and 3 from the NASA 6 and Mir-25 missions in1997-98. Calcium absorption after 100-120 days of flight

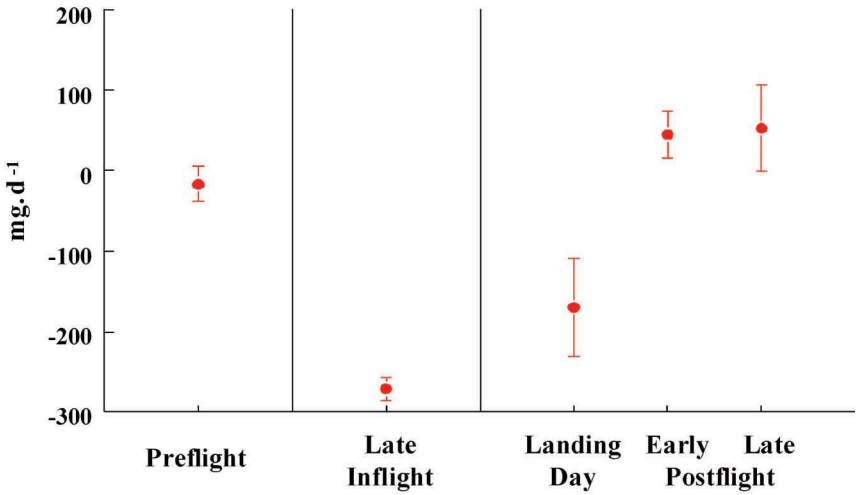
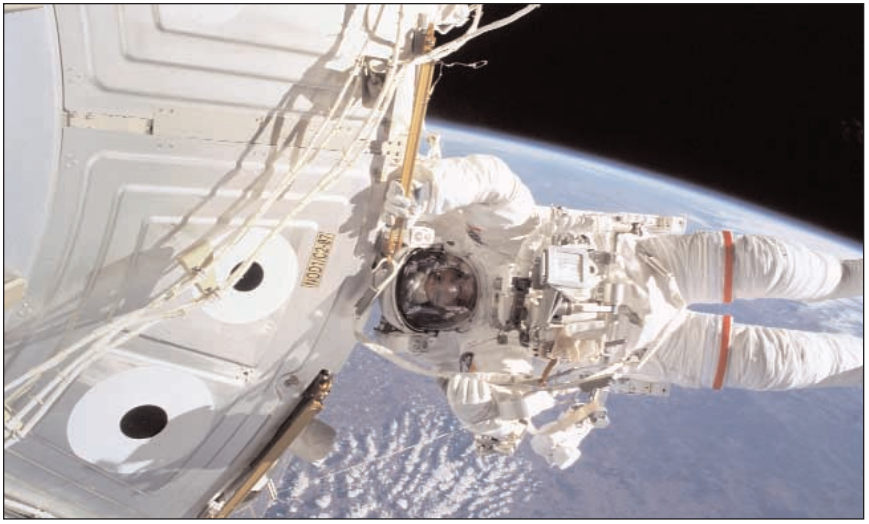


Figure 4. Mir 18 Bone Calcium Balance (Reference 7)

was substantially lower than measurements obtained preflight (7). Furthermore, absorption did not return to preflight levels until 3 months after return to Earth (7). Bone calcium balance, the net difference between deposition and resorption, exceeded -250 mg/d when measured during the last weeks of flight. If that rate is constant, astronauts



would lose approximately 7.5 g of calcium from their bones each month of flight. After return to Earth, bone calcium balance was +60 to +70 mg/d (7). Extrapolation of these data suggest that regaining the lost bone would require about 3 or 4 times the mission duration.

We have previously demonstrated that measurements of calcium can be made from saliva samples (10), a practice that helps to minimize the amount of blood needed for these studies. Saliva samples are easier to collect and process on a spacecraft than are blood samples, since neither phlebotomy nor centrifugation is required.

Space Shuttle

Further studies are required to define the time-course and metabolic consequences of bone loss during spaceflight. Calcium kinetic studies are planned for Shuttle flights beginning with STS-107 in the year 2002.

Stable isotope tracers will be administered before, during, and after flight, with biological samples collected for several days after each tracer administration. Biochemical and endocrine markers of bone metabolism will also be

measured. Dietary intake and sample collections will be recorded using a specially programmed bar code reader.

Research Team

The research team for these experiments includes both NASA and university scientists. Dr. Scott M. Smith is the lead for NASA's Nutritional Biochemistry Laboratory (NBL) at the Johnson Space Center. The NBL team will be responsible for the implementation of these studies, as well as the analysis of the biochemical, endocrine, and dietary data. Dr. Kimberly O'Brien (Johns Hopkins University) and Dr. Steve Abrams (Baylor College of Medicine) will analyze stable isotopes in the biological samples. Dr. Meryl Wastney (Metabolic Modeling Services, Ltd.) will conduct the mathematical modeling.

Future Plans

The Calcium Kinetics experiment is scheduled to be conducted on an additional Shuttle flight after the completion of the STS-107 mission. These short-term studies will allow us to better understand the initial adaptation to weightlessness. This experiment has also been developed for longer-duration missions and we hope to be able to implement it on board the International Space Station.

Summary

The experiment described here will provide valuable insight into the mechanisms and time-course of spaceflight-induced changes in calcium metabolism. Specifically, the studies will identify sites of calcium perturbation (e.g., intestine, kidney, bone), the degree and temporal nature of the change at each site, and the rate of restoration at the perturbed sites, by comparing metabolism before, during, and after flight. The results from these studies will complement previous work by

expanding both the number of subjects and the detail of the collection procedures. Information gained from these experiments will be critical for monitoring and counteracting the loss of bone mineral during flight. Finally, these results from this study may also further our understanding of the causes of and treatments for bone diseases on Earth, such as osteoporosis.

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